

Complex ovarian cysts in postmenopausal women are not associated with ovarian cancer risk factors

Preliminary data from the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial

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OBJECTIVE: We assessed whether asymptomatic ovarian abnormalities detected on ultrasonography in postmenopausal women are precursors to ovarian cancer.

STUDY DESIGN: We compared the transvaginal ultrasonographic findings from the initial examination of 20,000 postmenopausal women enrolled to date in an ongoing randomized trial of cancer screening with data on the established risk factors for ovarian cancer obtained from self-administered questionnaires. We distinguished cysts with the suggestive characteristic(s) of a septum, a solid component, or an irregular or thick wall ("complex cysts") from simple sonolucent cysts with none of those features.

RESULTS: High parity, a strong ovarian cancer protective factor, was negatively associated with complex cysts (odds ratio for ≥ 5 births vs no births, 0.72; 95% confidence interval, 0.53-0.97), but long-term oral contraceptive use, another strong ovarian cancer protective factor, was not associated with complex cysts (odds ratio, 0.96; 95% confidence interval, 0.76-1.20). A family history of ovarian cancer or multiple breast cancers, a strong risk factor for cancer, was not associated with complex cysts (odds ratio, 0.99; 95% confidence interval, 0.68-1.44). Other abnormalities found on ultrasonography (including simple cysts, bilateral cysts, or all abnormalities combined) also did not share the established risk factors for ovarian malignancy. We did not identify any combination of features of abnormalities (septum, echogenicity, size, or papillary projections) that manifested the cancer risk factor profile.

CONCLUSIONS: Although a very small proportion of the clinically silent ovarian abnormalities found on ultrasonography are determined to be ovarian cancers, the remaining complex cysts and other clinically suspicious abnormalities do not appear to be the immediate precursors of ovarian cancer. The eventual identification of such precursors will yield opportunities for earlier diagnosis, screening of high-risk groups, and better understanding of the cause of this often lethal malignancy. (*Am J Obstet Gynecol* 2000;183:1232-7.)

Key words: Ovarian cancer, ovarian cysts, epidemiology, ultrasonography, screening, precursors

Five-year relative survival in patients with ovarian cancer in the United States is only 47%.¹ Survival varies from 93% in localized disease to 28% in disease with distant

metastases, so the detection of ovarian cancer through screening offers great promise if otherwise lethal cancers can be detected earlier and treated more successfully. The effectiveness of such screening has not yet been clearly demonstrated,² and several large trials are underway.^{3, 4} In addition, the identification of premalignant lesions or precursors to ovarian cancer warrants attention to identify women at risk and to further fundamental understanding of ovarian carcinogenesis.⁵

The precursors to ovarian malignancy have not been identified, but reasonable candidates include the nonmalignant ovarian abnormalities detected in symptom-free

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postmenopausal women by transvaginal ultrasonography. This imaging technique allows measurement of the size of each ovary and visualization of cysts and other areas of abnormal density. Some of the nonmalignant abnormalities identified by ultrasonography, which are false-positive findings in the screening for cancer, may be precursors of ovarian cancer. If so, the abnormalities would be found more often in women with the established risk factors for ovarian cancer.⁶ For example, nulliparous women with a family history of cancer and no history of oral contraceptive use are at high risk of having ovarian cancer and therefore ought to be more likely to have ovarian cancer precursors. To search for potential precursors, we compared the known risk factors for ovarian cancer with ultrasonographic findings in an ongoing trial of cancer screening in postmenopausal women.

Material and methods

We studied all women who had enrolled in the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial⁴ at the time of analysis. This is a preliminary analysis from the ongoing trial, in which 78,000 women are expected to be enrolled in total. The trial is being conducted at the following 10 medical centers in the United States: University of Colorado Health Sciences Center, Denver; Georgetown University Medical Center, Washington, DC; Pacific Health Research Institute, Hawaii; Henry Ford Health System, Detroit; University of Minnesota School of Public Health, Minneapolis; Washington University School of Medicine, St Louis; University of Pittsburgh Cancer Institute; University of Utah School of Medicine, Salt Lake City; Marshfield Medical Research and Education Foundation, Wisconsin; and University of Alabama at Birmingham.

To be eligible to enter the trial, women had to be 55 to 74 years old and have had no previous diagnosis of colon, lung, or ovarian cancer. They were not eligible if they were undergoing cancer treatment or were enrolled in another screening or prevention trial. (Women taking tamoxifen were not enrolled at the time of analysis; subsequently they were allowed to enroll.) Most of the participants (92.8%) reported their ethnicity as white, 3.5% as Asian, 3.0% as black, and 0.6% as Pacific Islander, American Indian, or Aleut. About 1% reported Hispanic ethnicity.

The participants were given a brief baseline questionnaire including family history of cancer; menstrual, reproductive, and contraceptive history; and gynecologic surgery. Infertility was defined as having tried to become pregnant without success for ≥ 1 year. Gynecologic surgery included tubal ligation, hysterectomy, and unilateral oophorectomy. Family history of cancers of the breast or ovary was limited to mother and sisters, because data on more distant relatives are less reliable. Participants completed this questionnaire either in the screen-

ing clinic or at home. The data were collected as pre-coded responses, and forms were optically scanned.

Half of the trial participants were assigned at random either to usual medical care or to a regimen of periodic cancer screening. The screening examination included bimanual ovarian palpation, transvaginal ultrasonography, and serum assay for the cancer antigen CA 125. Trained examiners conducted the ultrasonography with a 5- to 7.5-MHz transvaginal probe. The examiner measured each ovary and recorded the number of abnormalities present. Ovarian volume was calculated as $0.523 \times \text{Longitudinal diameter} \times \text{Transverse diameter} \times \text{Anteroposterior diameter}$. For the 3 largest discrete cysts or abnormalities the examiner recorded the maximum diameter, noted the presence of solid areas and septa, and characterized the cyst outline, cyst wall thickness, and echogenicity on a 5-point scale. The examiner also summarized the ultrasonographic results as normal, suggestive of cancer, abnormal but not suggestive of cancer, or inadequate. The findings were deemed suggestive of cancer if either ovarian volume exceeded 10 cm^3 or if any solid area, papillary projection, or mixed solid-cystic component was seen. (During the early months of the trial, examiners did not record abnormalities $< 2 \text{ cm}$ in diameter; therefore some ovaries classified as normal in this analysis may have had very small cysts detected.)

The screening center staff referred the participant for further evaluation if the sonogram was suggestive of cancer, if the ovarian palpation findings suggested abnormalities, or if the serum CA 125 level exceeded 35 U/mL . The personal physician's evaluation of a woman referred after screening is not part of the trial protocol and is not standardized. Study staff request follow-up information for all women referred for evaluation, but these data are not yet available for analysis. At the time of analysis ovarian cancer had been diagnosed in 20 women; they were excluded from this analysis, which focuses on precursors rather than cancer itself.

At the time of analysis the ultrasonographic and baseline questionnaire data were available for 20,355 women; 471 women (2%) were excluded because of inadequate examinations or because of errors or missing data in the documentation of examination findings; 19,884 women were included in the analyses. We compared risk factors to abnormalities, using correlation analysis and estimation of prevalence odds ratios and 95% confidence intervals from unconditional logistic regression.⁷ Subjects with data missing on ≥ 1 risk factor were excluded from individual analyses of those risk factors.

Results

The examiner visualized ≥ 1 ovary in 11,433 women, or 57% of the total number of women screened, and both ovaries were seen in 6688 of these women. Although ovaries that are not seen are presumably unlikely to have

Table I. Percentage of women with one or both ovaries visualized on ultrasonography

	Women		
	Ovaries visualized (No.)	Total No.	%
Age at examination			
55-59 y	3,519	6,076	58
60-64 y	3,898	6,621	59
65-69 y	2,587	4,540	57
70-74 y	1,429	2,647	54
Age at menopause			
<40 y	1,212	2,529	48
40-44 y	1,287	2,533	51
45-49 y	2,637	4,511	58
50-54 y	4,746	7,781	61
≥55 y	1,451	2,383	61
Parity			
0	983	1,631	60
1	744	1,355	55
2	2,546	4,422	58
3	2,846	4,924	58
4	2,019	3,534	57
≥5	2,269	3,983	57
Previous gynecologic surgery*			
None	6,747	11,003	61
One ovary removed	705	1,669	42
Hysterectomy	2,130	4,138	51
Tubal ligation	1,833	3,044	60
Body mass index			
19-20.9 kg/m ²	815	1,380	59
21-22.9 kg/m ²	1,800	2,968	61
23-24.9 kg/m ²	2,146	3,559	60
25-26.9 kg/m ²	1,970	3,313	59
27-28.9 kg/m ²	1,478	2,597	57
29-34.9 kg/m ²	2,156	3,955	54
35-50.0 kg/m ²	757	1,496	51
All women	11,433	19,884	57

*Classified as follows: one ovary removed (with or without hysterectomy or tubal ligation); hysterectomy with ovaries preserved (with or without tubal ligation); tubal ligation only; or no oophorectomy, hysterectomy, or tubal ligation.

tumors, whether they harbor cancer precursors is unknown. We restricted the risk profile comparisons to women with visualized ovaries. The median volume for visualized ovaries was 1.1 cm³ overall, with an expected age gradient, from 1.3 cm³ in women <60 years old to 0.9 cm³ in women ≥70 years old.

As shown in Table I, the sonographers were least likely to visualize one or both ovaries in women aged 70 to 74 years. The sonographer's ability to visualize the ovaries rose substantially with the participant's age at menopause, from 48% in women who stopped menstruating at or before the age of 40 years, to 61% in those who stopped at age 55 years or later. Parity was not consistently related to visualization. Women who reported a unilateral oophorectomy were less likely to have the other ovary seen. It was more difficult to visualize one or both ovaries in women with higher body mass index.

Overall the sonographer recorded some morphologic abnormality in 21% of the women whose ovaries were vi-

Table II. Prevalence (percentage) of ovarian abnormalities on ultrasonography, according to age at examination, age at menopause, family and personal history of breast cancer, and history of infertility

	Cyst(s) (%)		
	Total	Simple*	Complex†
All women combined	21.2	15.7	5.5
Age at examination			
55-59 y	24.4	18.2	6.2
60-64 y	19.3	14.0	5.3
65-69 y	19.6	14.6	5.0
70-74 y	21.2	15.9	5.3
Age at menopause			
<40 y	35.3	27.7	7.6
40-44 y	26.6	19.4	7.2
45-49 y	17.2	12.7	4.4
50-54 y	18.0	13.3	4.7
≥55 y	22.0	15.2	6.9
Family history			
No ovarian or breast cancer	20.8	15.4	5.5
Breast cancer only	23.6	17.8	5.7
Ovarian cancer only	20.4	14.2	6.2
Breast and ovarian cancer	26.9	22.4	4.5
Prior breast cancer			
No breast cancer	21.3	15.8	5.6
Breast cancer	17.7	13.3	4.4
Infertility history			
Yes, nulliparous	26.6	17.2	9.4
Yes, parous	23.9	18.1	5.8

*Sonolucent abnormality with no solid area, no septum, and a thin, smooth wall.

†Cyst with at least one of the following characteristics: some solid area; a septum; or a thick wall or an irregular wall.

sualized. We classified women according to the worst abnormality present in either ovary. Five percent had at least one "complex cyst"—an abnormality such as a thick wall, a papillation, a septum, an echogenic portion, or some solid component. Sixteen percent had only simple sonolucent cysts with no solid component, no septum, and a smooth, thin wall.

Table II compares the prevalence of all abnormalities combined, of simple cysts, and of complex cysts to 5 host factors associated with an increased risk of having ovarian cancer—age, age at menopause, a family history of breast or ovarian cancer, a prior breast cancer, and a history of infertility.⁶ Prevalence of immediate precursors ought to be positively associated with these factors. Older age at examination, which is positively associated with cancer risk, was weakly negatively related to the prevalence of abnormalities. Women with later menopause, who may have a slightly increased cancer risk, were somewhat less likely to have complex cysts and substantially less likely to have simple cysts. Women who reported breast cancer in a mother or sister (at moderately elevated ovarian cancer risk) were slightly more likely to have complex cysts and simple cysts. Those who reported ovarian and breast cancer in the family (at highest risk) were more likely to have simple cysts and less likely to have complex cysts than

were women with no ovarian or breast cancer in their families. Breast cancer survivors, whose risk of having ovarian cancer is increased, were about as likely as other women to have either type of abnormality. Nulliparous women reporting a history of infertility were more likely to have complex cysts. Thus the women at higher risk of having ovarian cancer showed no consistent pattern of a higher prevalence of complex or simple cysts.

Table III shows the prevalence of abnormalities according to 3 protective factors known to reduce risk of ovarian cancer—total number of births, duration of oral contraceptive use, and history of gynecologic surgery. Parous women, who were at a lower risk of cancer, had fewer complex cysts than did nulliparous women, but the total number of births was not related to the presence of abnormalities. Women who had taken oral contraceptives for ≥ 5 years were more likely to have simple cysts and less likely to have complex cysts. Gynecologic surgery (including tubal ligation or hysterectomy with preservation of one or both ovaries) has been consistently linked to a decreased risk of ovarian cancer, although the explanation of this association is not clear. Women who reported prior gynecologic surgery had more abnormalities seen on ultrasonography. In this extremely large sample size the prevalence of complex or simple cysts was statistically significantly associated with every variable shown in Tables II and III, albeit with no consistent pattern or with patterns in the reverse of the predicted direction.

Table IV shows the estimated prevalence odds ratios for simple cysts and complex cysts according to major factors, with each adjusted for the effects of the others and the effects of age, as derived from multiple logistic regression models. Women reporting ovarian cancer or multiple breast cancers in their family were no more likely than women with a negative family history to have either simple (odds ratio, 1.03) or complex (odds ratio, 0.99) ovarian cysts. (In general, women reporting ovarian cancer or multiple breast cancers in their first-degree relatives face about a 3-fold risk of having ovarian cancer, in comparison with women having neither cancer in the family; women with a single breast cancer in a first-degree relative face an intermediate risk.) Women ≥ 60 years old were slightly less likely than younger women to have simple or complex cysts, but no age gradient appeared for either type of cyst. (In general, ovarian cancer risk is half again as high at age 70-74 years compared with age 55-59 years.) With increasing parity women were slightly more likely to have simple cysts and slightly less likely to have complex cysts. The association between complex cysts and parity was statistically significant. The duration of oral contraception was weakly related to simple cysts and unrelated to complex cysts. (In general, ovarian cancer risk is halved in women with high parity or long-term oral contraceptive use.)

In Table IV the analysis is repeated with separate calcu-

Table III. Prevalence (percentage) of ovarian abnormalities on ultrasonography, according to gynecologic surgery, parity, and oral contraception

	Cyst(s) (%)		
	Total	Simple*	Complex†
All women combined	21.2	15.7	5.5
Births (No.)			
0	21.7	14.0	7.6
1-2	21.3	15.1	6.2
3-4	21.0	16.3	4.7
≥ 5	21.2	15.8	5.4
Oral contraception			
Never used	20.2	14.8	5.4
Used < 5 y	22.0	16.2	5.9
Used ≥ 5 y	22.2	16.9	5.2
Gynecologic surgery‡			
No surgery	17.3	12.3	5.0
One ovary removed	28.4	20.0	8.4
Hysterectomy (ovaries retained)	34.8	27.8	7.0
Tubal ligation only	17.0	12.3	4.7

*Sonolucent abnormality with no solid area, no septum, and thin, smooth wall.

†Cyst with at least one of the following characteristics: some solid area; a septum; or a thick wall or an irregular wall.

‡Classified as follows: one ovary removed (with or without hysterectomy or tubal ligation); hysterectomy with ovaries preserved (with or without tubal ligation); tubal ligation only; or no oophorectomy, hysterectomy, or tubal ligation.

lations for black women and for white women. We found no statistically significant differences, but parity was positively correlated with complex cysts in black women and negatively correlated in white women.

We analyzed the data as in Table IV, considering the ovaries that were not visualized to be normal. Parity was still statistically significantly associated with a lower prevalence of complex cysts (odds ratio, 0.75, 0.58, and 0.68 for 1 or 2, 3 or 4, and ≥ 5 births, respectively; $P < .01$). Oral contraceptive use was weakly and not statistically significantly related to complex cysts (< 5 years: odds ratio, 1.01; 95% confidence interval, 0.84-1.22; ≥ 5 years: odds ratio, 0.90; 95% confidence interval, 0.71-1.12). Women with ovarian cancer or multiple breast cancers in first-degree relatives had complex cysts no more often than did women with no breast or ovarian cancer in the family (odds ratio, 0.97; 95% confidence interval, 0.67-1.40).

We also examined the risk profiles of other groups of women, including those with any abnormality, with multiple simple cysts, with complex cysts defined in various ways, or with bilateral abnormalities (data not shown). The risk factor profiles varied slightly, but none of the women showed a profile similar to that of ovarian cancer. For instance, bilateral abnormalities were associated with age, infertility, and oral contraception in the predicted directions but were related to a family history of breast or ovarian cancer, gynecologic surgery, and parity in the opposite directions.

Table IV. Adjusted prevalence odds ratio estimates and 95% confidence intervals for simple and complex cysts according to major ovarian cancer risk factors

<i>Risk factor</i>	<i>Simple cyst(s)</i>		<i>Complex cyst(s)</i>	
	<i>Odds ratio*</i>	<i>95 % Confidence interval</i>	<i>Odds ratio*</i>	<i>95 % Confidence interval</i>
History				
No family breast or ovarian cancer	1		1	
One breast cancer in family	1.24	1.07-1.44	1.12	0.88-1.43
Ovarian or multiple breast cancers	1.03	0.81-1.30	0.99	0.68-1.44
Age				
55-59 y	1		1	
60-64 y	0.72	0.63-0.82	0.81	0.66-0.99
65-69 y	0.76	0.66-0.88	0.76	0.60-0.96
70-74 y	0.85	0.71-1.01	0.84	0.63-1.12
Parity				
No births	1		1	
1-2 births	1.03	0.84-1.27	0.79	0.60-1.04
3-4 births	1.15	0.95-1.41	0.61	0.46-0.80
≥5 births	1.16	0.93-1.43	0.72	0.53-0.97
Oral contraceptive use				
None	1		1	
<5 y	1.05	0.93-1.19	1.07	0.88-1.30
≥5 y	1.11	0.96-1.28	0.96	0.76-1.20

*Prevalence odds ratio estimate, adjusted for age and for the other factors shown.

We also compared each of the 8 risk or protective factors shown in Tables II and III with each of the detailed morphologic features recorded from the ultrasonographic image, specifically, the presence of any solid area, the presence and thickness of a septum, the presence of papillation or irregularity in the cyst wall, and the degree of echogenicity (data not shown). The presence of any solid area and the degree of echogenicity, which were correlated, rose with infertility and with lower parity but not with other risk factors. The presence of a septum was correlated with older age at examination and with later menopause but not with other risk factors.

Comment

Several goals motivate the search for detectable precursors to ovarian cancer. The presence of such precursors might define high-risk women who should be screened for cancer frequently. The precursors themselves and the women with them might be studied in various ways to illuminate ovarian cancer's natural history. To date, 3 types of abnormalities have been examined as potential precursors. First, clinically apparent functional ovarian cysts, which are predominant before menopause, have been studied and found to have determinants that are distinctly different from those of ovarian cancer.⁸ Second, microscopically visible features of the ovarian surface, notably, inclusion cysts, were suggested as precursors in early reports but were not confirmed.⁹ Third, recent studies report p53 mutations and other molecular characteristics in ovarian tissue that adjoins malignancy.¹⁰ Such mutations also have been reported to correlate with the lifetime number of ovulations, a summary measure

that reflects the protection seen for pregnancy and years of oral contraceptive use.¹¹

In this study we looked for cancer precursors among the morphologic abnormalities detected on transvaginal ultrasonography. Such abnormalities do not produce clinical symptoms but can be detected without the invasive procedures needed to examine the microscopic features of the ovarian epithelium or molecular derangements. Thus it was possible to collect data on healthy postmenopausal women who volunteered for the Prostate, Lung, Colon, and Ovarian Cancer Screening Trial. The thousands of ultrasonographic examinations conducted for the detection of early cancer revealed many other abnormalities. We compared the presence of these silent, nonmalignant morphologic abnormalities to the established risk factors for ovarian cancer in the hope of detecting a type of abnormality that showed the same risk factor profile as ovarian cancer itself. We specifically examined cysts with a septum, a thick or irregular wall, or any solid component ("complex cysts").

Complex cysts were less prevalent in women of high parity, but age, oral contraceptive use, and family cancer history were unrelated to prevalence. Indeed, although one or more types of abnormality were weakly related to one or more of the established risk factors, no individual type of abnormality and no group of abnormalities resembled ovarian cancer in its epidemiologic profile. In general, it is to be expected that ovarian cancers constitute only a small fraction of the abnormalities seen on ultrasonography; the current data suggest that cancer precursors also are rare and mingled in with harmless abnormalities not closely linked to the causes of ovarian cancer.

These data offer little support for a simple model of ovarian carcinogenesis in which genetic predisposition and number of ovarian epithelial cell replications (as measured by age, parity, and oral contraception) influence the risk of having complex ovarian cysts, some of which progress to cancer. In this respect ultrasonographically detected abnormalities do not relate to ovarian cancer in the patterns seen for infection with human papillomavirus, cervical dysplasia, and cervical cancer; for colon polyps and colon cancer; or for dysplastic nevi and melanoma. A more subtle model or a different definition of a precursor lesion appears to be required.

Is there an alternative explanation in which complex cysts are cancer precursors but are unlinked to the cancer risk factors? Suppose the majority of cancers that would have arisen over the 16-year course of the trial (in the absence of screening and intervention) would have arisen largely among the 5% of women with complex cysts at the baseline examination. Cancers would be expected to occur in 1% or 2% of higher-risk women and in 0.5% or 1% of lower-risk women. Thus a very high proportion of the complex cysts would give rise to cancer; furthermore, age, parity, and oral contraception all would exert strong effects on cancer risk in the presence of complex cysts and weak effects otherwise. This model implies that oral contraception and parity, typically complete by age 45 years, exert their undisputed effects on risk not by causing complex cysts but by acting on complex cysts that were caused by factors unrelated to ovarian cancer risk. Such a scenario is possible but cannot be assessed directly because the trial alters the natural history by design.

Various limitations in the study could have influenced the results. It is possible that an ultrasonographically detectable precursor exists but that this study failed to find it because some unrecognized or unrecorded features of the ultrasonographic image define the precursor. If a precursor lies in the ovaries that are not seen on ultrasonography or if the ultrasonographic imaging was of very poor quality, these data could obscure the existence of a strong precursor. Similarly, if some subtle combination of recorded features defines a precursor (eg, echogenic but thin-walled), this analysis could have missed it.

These issues may not be resolved, but they will be clarified as clinical trials progress.^{3, 4} For example, longitudinal data from successive screening may reveal whether the presence of new cysts or a change in existing cysts

constitutes a cancer precursor. In addition, as the genetic markers of premalignancy are elucidated, it may be possible to locate precursors by combining the risk profile approach taken here with other data comparing morphologic features seen on ultrasonography to genetic markers in tissue taken from the visualized ovaries. In addition, observational studies of ovaries from women at high risk and of very early ovarian cancers may disclose precursors. The search for precancerous lesions ought to continue.

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